REVIEW

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Future VIROLOGY

Hepatitis B: prevention, protection and occupational risk

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ABSTRACT Since 1992, the inclusion of HBV vaccination has been recommended by the WHO for all immunization programs implemented by nations. In Europe, the introduction of HBV vaccination has markedly reduced the incidence of acute HBV, and before the introduction of HBV vaccine, healthcare workers (HCW) were at considerable risk of infection. The present review discusses the main problems regarding three fundamental issues in hospital settings: prevention of HBV in HCW, protection induced by vaccination (problems regarding nonresponders) and risk for HCW exposed to blood-borne pathogens (occupational risk). The screening of HBV markers plays a decisive role in evaluating the degree of immune coverage in subjects exposed to biological risk and permits an increase in immune coverage through vaccine implementation.

KEYWORDS
• hepatitis B infection • occupational risk • prevention • protective antibodies • vaccination

HBV infection is a significant biological risk for healthcare workers (HCW), as HCW are exposed to human fluids and consequently to blood-borne pathogens. Prior to the introduction of the vaccination against HBV, the risk of infection was three- to five-times higher in HCW than in the general population, with vaccination and the application of standard precautions contributing to reduce this risk [1].

Since 1992, the inclusion of hepatitis B vaccination has been recommended by the WHO in all immunization programs implemented by nations. Indeed, the introduction of HBV vaccination in Europe has markedly reduced the incidence of acute infection.

The introduction of mandatory HBV vaccination in Italy (law 165/1991) has contributed to reducing the incidence of the disease, even in the age group with the highest incidence (15–24 years old), which is largely related to the abuse of parenteral drugs and/or exposure to other risk factors such as unsafe sexual contact [2].

The present review intends to highlight the problem of the occupational risk for HCW according to three main items: the prevention of HBV infection (efficacy of vaccination); the protection against HBV infection, discussing both problems related to waning antibodies and those related to nonresponders; and the reduction of occupational risk.

Prevention

HBV vaccination campaigns using a plasma-derived vaccine began in several countries in the early 1980s. In 1986, a genetically engineered *Saccharomyces cerevisiae* yeast recombinant vaccine replaced the plasma-derived vaccine. Nationwide intervention reduced new HBV infections and HBV-related mortality within less than two decades, and several countries have achieved a low endemicity status [3,4].

Mandatory vaccination was introduced in Italy in 1991, with a vaccination schedule that included 3-month-old children (at 3, 5 and 11 months of age) and 12-year-old adolescents (at time 0 and after

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1 and 6 months). This program ensured that the cohorts overlapped 12 years later; the vaccination of adolescents was discontinued in 2003 [4]. However, WHO recommends child immunization with a dose within 24 h after birth and second and third doses with an interval of at least 4 weeks, primarily in high-endemicity countries [5]. Moreover, the policy of distinct European countries is quite different because the age of vaccine administration is variable. As described in **Table 1**, some countries vaccinate at birth and others at 2–3 months of age [6]. There are also differences with regard to the behavior of European countries to declare HBV vaccination as mandatory or only recommended **(Table 1)** [7].

Vaccination against HBV is not mandatory in Italy for HCW, though it is offered for free; this is in contrast to the schedules initially adopted for tetanus vaccination (law 292/63), introduced at first as mandatory for at-risk workers and only later for newborns. This policy has led to a noticeable difference in immunization coverage among HCW born before or after the mandatory introduction of the vaccination [8].

Two recombinant HBV vaccines were employed until polyvalent vaccines became available in 2000: Engerix-B® (10 µg dose) was initially used (until 1993) and Recombivax HB® (5 µg dose), both at a pediatric dose up to 15 years of age.

Epidemiological surveillance has shown that recombinant vaccines are safe. Indeed, the results from several scientific reports definitively exclude vaccine-induced neurological disorders [9–11].

Despite the substantial rates of immunization coverage achieved by vaccination programs, a subset of the vaccinated population is considered to be less protected or nonresponding.

In the next section, the levels of protection induced by the HBV vaccine are discussed.

Protection

The International Standards define as protective an antibody level (anti-HBs) higher than 10 IU/l after the primary vaccine series [12,13].

Following the introduction of universal vaccination against HBV, one major issue is the persistence of protective antibodies and the duration of immunity after the primary series, particularly in low endemicity countries where no natural boosters are administered [14,15]. Long-term study in Europe has shown that immune memory induced by the HBV vaccine persists for more than 15 years; thus, the booster vaccination

Table 1. HBV vaccination survey in some European countries according to age of first vaccine dose and in relation to the modality of implementation.

Country	Age of first dose	Implementation
Belgium	2 months	Recommended†
Bulgaria	At birth	Mandatory
Cyprus	2 months	Recommended
Czech Republic	3 months	Mandatory
Estonia	At birth	Recommended
France	2 months	Recommended†
Germany	2 months	Recommended
Hungary	At birth	Mandatory
Ireland	2 months	Recommended
Italy	3 months	Mandatory
Latvia	At birth	Mandatory
Lithuania	At birth	Recommended
Luxembourg	2 months	Recommended
Malta	15 months	Recommended
Poland	At birth	Mandatory
Portugal	At birth	Recommended
Romania	At birth	Mandatory
Slovakia	2 months	Mandatory
Slovenia	Before school	Mandatory
Spain	2 months	Recommended

Denmark, Finland, Iceland, The Netherlands, Norway, Sweden and UK have a selective immunization program for at-risk subjects.
†Mandatory for at-risk subjects only.
The data are derived from [6] and [7].

is considered as unnecessary in immunocompetent subjects [16].

The persistence of circulating antibodies and the significance of antibody levels that are positive but lower than 10 IU/l are of clinical relevance and not yet fully clarified [17]. In fact, the group of subjects with circulating antibodies below 10 IU/l includes both individuals with immunological memory already after vaccination and therefore able to potently respond to the booster or to HBV exposure and individuals without immunological memory against the virus and thus 'nonresponders'. In this scenario, it is an absolute requirement to clarify the persistence of immunological memory after vaccination despite decreases in circulating antibodies. In HCW, a booster dose would enable the determination of immunological memory for an effective response to viral load. In fact, even individuals with waning anti-HBs antibodies show intact T-cell and B-cell immunologic memory several years after vaccination [18] because the memory B lymphocytes that produce the anti-HBs antibodies do not decline [19].

A high percentage of subjects checked for anti-HBs antibodies exhibited levels higher than 10 IU/l more than 10 years after vaccination, confirming the long-lasting duration of HBV immunological coverage after the vaccine [13,15,16,20–24]. Remarkably, antibody levels less than 10 IU/l were detected in subjects with a shorter interval since the primary series, suggesting that the persistence of the antibodies could be influenced by the vaccine employed [24]. In fact, subjects vaccinated with Engerix-B had a higher rate of protective antibodies and higher antibody levels than a group of subjects vaccinated with Recombivax HB [24], confirming that the Engerix-B vaccine has a greater efficacy [25–27]. The different dose of antigen between the two types of vaccine (10 µg dose for Engerix-B, 5 µg dose for Recombivax HB) may be a reasonable explanation for this phenomenon and is supported by the case of hexavalent Hexavac®, which was suspended by the European Medicines Agency owing to underdosing (5 µg) due to the low immunogenicity of the HBV component [28].

Several studies noted that the persistence of immunological memory is longer than that of circulating antibodies [13,24,29]; HBsAg-specific memory persistence is due to T-lymphocyte activation (presentation of the original HBsAg epitopes) after clonal proliferation of the T-cell population [30].

A nonresponse to HBV vaccine is attributed to several mechanisms, such as inadequate Th1- and Th2-like cytokine production [31]. Moreover, *HLA-DRB1*07* and immunoregulatory cytokine gene polymorphisms correlate with variable immune responses to recombinant vaccine [32]. Specific SNPs in genes encoding cytokines (cytokine receptors) and *TLR2* have been associated with protection induced by HBV vaccine, and the AG haplotype defined by SNPs rs1 143633 (IL-1B; intron) and rs1 143627 (IL-1B; intron) has been more frequently identified in nonresponders [33]. Similarly, changes in *CXCR5* expression are associated with polymorphisms in follicular helper T cells and correlate to no-response [34], and polymorphisms in the IL-4 gene could play a pivotal role in the response to HBV vaccine [35]. Furthermore, nonresponse to HBV vaccination may be associated with an higher frequency of the TT genotype of the *IFNG* (+874 T/A) gene polpolymorphism and intronic (CA)n polymorphic microsatellite marker of the *IFNGR1* gene [36].

The loss of immune memory is due to a low production of antibodies (<10 IU/l) after a booster dose [37], and immune memory is in fact revealed by the ability to induce an anamnestic response after a booster dose [4,38]. Immunologic memory in peripheral blood mononuclear cells of children vaccinated as infants showed persistence at least 5 years after vaccination due to T-cell proliferation and their secretion of IFN-γ when cultured with HBsAg [39]. Notably, several seronegative individuals have immunologic T-cell memory, and their T cells are able to produce anti-HBs antibodies when their B cells are activated by a booster [18]. In contrast, nonresponders to vaccination show a suboptimal B-cell response [40].

Circulating antibodies rapidly wane after vaccination at birth [14,41]; however, it has recently been shown that vaccination before 1 year of age results in a larger number of subjects with antibody levels lower than 10 IU/l when monitored in adulthood compared with a cohort monitored at the same time interval from the first vaccination series but vaccinated after 1 year of age [42]. Accordingly, the real requirement of a booster vaccination to sustain protection does not have a general consensus in Europe, as in all areas with higher endemicity [15,16,21]. The European Consensus Group [43] stated that routine boosters are unnecessary to maintain long-term protection in vaccinated immunocompetent individuals.

Other factors are involved in the induction of nonprotective antibodies, such as immunosuppression, low weight (<1 kg) at birth, smoking, extreme obesity, male gender, age over 50 years [13,25,44–46] and age at the primary series [42]. Regarding age as a cause of a low response, it is clearly demonstrated that vaccination at 3 months compared with after 1 year of age and considering the same interval since vaccine causes a higher number of subjects with antibody levels less than 10 IU/l (47.2 vs 17%, respectively) and a significantly lower antibody titer [48].

The persistence of antibodies after vaccination and the anamnestic response to a booster dose in children vaccinated with pediatric doses and subjects vaccinated as adolescents with adult doses have also been studied [4]. The results showed that both cohorts had a persistence of immunological memory after a 10-year follow-up, suggesting that booster doses are unnecessary to guarantee long-term protection. In low endemicity countries, the vaccination schedule would produce the persistence of protective antibodies without a booster.

As already depicted, the loss of circulating antibodies does not necessarily signify the loss of protection. The long incubation period of HBV allows the immunological memory sufficient time to develop an adequate level of antibodies to respond to the viral load [28]. Accordingly, a relevant issue is whether to establish the persistence of immunological memory when circulating antibodies vanish after the primary series.

The anamnestic response is defined as 'an increase in anti-HBs concentration of four-times or more after the booster vaccine or providing an antibody concentration of at least 10 IU/l after the booster' [47], whereas the booster itself has been defined as a 'vaccination given some time after primary vaccination series with the aim of providing protective immunity/protection against significant breakthrough infection' [20,26].

Within this framework, the threshold of 10 IU/l appears useful for evaluating the response after a booster, but is not useful for predicting the response to the booster [24]. Consistently, another study [29] demonstrates that a level higher than 1 IU/l is sufficient to predict a booster response, supporting the persistence of immune memory in past-vaccinated individuals. Furthermore, post-booster response and the pre-booster anti-HBs level are closely related: subjects having pre-booster antibody levels below 0.1 IU/l have likely low or no response to the booster [24]. As a consequence, a new level of protection at an antibody level of 2 IU/l has been suggested [24]. Subjects with low or no response to the booster will benefit from a new full vaccination series; in the case of insufficient antibody production, these individuals would be considered 'nonresponders'. If these individuals are HCW, caution should be employed in high-risk procedures.

All these findings require an accurate evaluation of the immunological status after the primary series of vaccination to develop an appropriate and effective vaccination strategy, with particular attention to subjects who function in high-risk scenarios, such as HCW.

Occupational risk

HCW are exposed to a variety of blood-borne pathogens by needlestick and sharp injuries or mucocutaneous contamination [48]. HBV, HCV and HIV are the most relevant pathogens transmitted in hospital settings. HBV is the most remarkable risk for HCW, and the introduction of the vaccination against HBV widely reduced the rate of infection [1].

Needlestick injuries are a common way of transmission of blood-borne pathogens to HCW, and the magnitude of the infection depends on the cause of the wound, that is, if it is caused by sharps or hollow-bore or suture needles. In fact, 22-gauge hollow-bore needles can inoculate an average volume of 1 µl, a quantity sufficient to contain up to 100 infectious doses of HBV [49]. A relevant issue in hospital settings is that a large number of injured subjects do not report accidents [50] and also do not complete follow-up, even though the source is positive or unknown [51].

It is well established that the seroconversion after needlestick or sharp injuries contaminated with an infected source is 10–30% for HBV, 4–10% for HCV and 0.1–0.3% for HIV; the probability of seroconversion depends on the volume of blood injected, the viral concentration and the route of administration [52]. However, HBV seroconversion is high (approximately 30%) if the source patient is HBe antigen (HBeAg) positive, though is less than 6% if the source is HBs antigen (HBsAg) positive [52]. Nonetheless, a 12-year Italian study detected no seroconversion for HBV, 0.36–0.39% for HCV and 0.14–0.43% for HIV [52].

Several studies have been published on needlestick and sharp injuries [50,53–57] and thus the prevention of biological exposure. Regardless, the transmission of pathogens by wounds or mucocutaneous contamination remains a relevant problem in healthcare settings.

Italian research on university workers showed a low prevalence (10%) of past history of HBV (documented by a marker assay). Among past-infected subjects, 8.8% showed positive anti-HBc antibodies only; furthermore, the prevalence of HBsAg was very low (1.1%) and even lower for HBeAg (0.2%) carriers. A significant prevalence of past-infected subjects was observed among those more exposed to the risk, such as workers in surgical areas. Moreover, a large number of susceptible subjects were also observed due to a low compliance to vaccination, which is not mandatory in Italy for subjects exposed to biological risk. Among university HCW, no subject was recognized as an HBeAg bearer, though three were positive for HBsAg; HBV DNA was absent or chiefly lower than 10^4 copies/ml. Thus, it is possible to state that there is a low possibility of HBV transmission from HCW to patients [58].

The prevalence of HIV and HBV infections has been investigated in an international cohort of dental hygienists, and the conclusions were that these HCW had a minimal risk of infection [59].

More interestingly, a high percentage (85.9) of students of an Italian medical school appeared to be anamnestically vaccinated; among these, 97.2% had a measurable antibody level, and only 2.8% were nonresponders. Overall, approximately 15% of the students appeared to be susceptible to HBV [60]. Among them, females showed a higher compliance to vaccination than males, but the most relevant result was the coverage by the relevant law; in fact, students covered by Italian law 165/91 on HBV vaccination showed a high compliance (90.7%) compared with the oldest students (50.9%) [60]. The number of vaccinated subjects appeared to be similar to other European experiences [61].

By 2003, 151 of 192 WHO member states had adopted a childhood HBV vaccination policy [62]. Differences in compliance may be related to differing vaccination policies. Curiously, to guarantee the right of privacy of workers, the Canadian Medical Association disagrees with mandatory vaccination against HBV and the postvaccination screening of exposure-prone HCW [63].

There are several reports [64] of HBV transmission to patients (six for HCV) from HCW, with more than 400 infected patients (14 by HCV transmission). The transmission rate was found to vary between 6 and 15%, but most of these occurred prior to 1991, before HBV vaccination was widely used and before standard (universal) infection control precautions were implemented [65]. According to these recommendations, infected HCW HBeAg carriers should not perform exposure-prone procedures.

Owing to the lack of HBV vaccination requirement for HCW, subjects not subjected to mandatory vaccination are rarely compliant with the vaccine [8]; therefore, compulsory routine vaccination appears necessary because suggestion only is not sufficient to ensure compliance with the schedule [8,66]. However, when offered to nonvaccinated subjects, seroconversion is high [8].

In 29 countries of the EU, implementation of mandatory vaccination for HCW is rare [67].

Another relevant issue is the management of HCW after biological exposure. The Advisory Committee on Immunization Practice recommends vaccination for all HCW who are unvaccinated or with incomplete vaccination, and suggests HBV immunoglobulins and vaccination to nonresponders and the unvaccinated and incompletely vaccinated after needlestick or sharp injury [68].

Conclusion

The eradication of HBV is a large challenge, and a tremendous effort is necessary to achieve this goal, particularly in hospital settings. Furthermore, the decrease in occupational risk following the large implementation of vaccination coverage does not allow for reducing efforts to combat this disease. Adherence to standard precautions and vaccination should be mandatory for HCW. As indicated by Poland [69], there are many behaviors at work that do not adhere to standard precautions, as clearly shown by Doebbeling *et al.* [70].

Another relevant point of discussion is represented by the possible transmission of bloodborne infections by HCW to patients. As well explained [64], high attention to this problem is necessary, and prone procedures should not be carried out by infected individuals, according to guidelines.

The nationwide vaccination implemented by the WHO is the first milestone to achieving the

Table 2. Recommendation for HBV vaccination for healthcare workers in some European countries.

Country	Implementation
Austria	Recommended
Belgium	Mandatory
Czech Republic	Mandatory
Denmark	Recommended†
France	Mandatory
Germany	Recommended
Ireland	Recommended
Italy	Recommended
Luxembourg	Recommended
Netherlands	Recommended
Norway	Recommended‡
Poland	Mandatory
Slovenia	Mandatory
Spain	Recommended
Sweden	Recommended
Switzerland	Recommended
UK	Recommended

†Only for medical and nursing staff.
‡Only for medical, nursing, and paramedical staff and for medical students.
The data are derived from [74].

objective of HBV eradication. The rapid decline in the incidence of HBV in Italy demonstrated after the introduction of mandatory vaccination [2] a tangible sign that vaccination is a decisive means for protecting population.

In conclusion, the attitude of HCW toward HBV vaccination is suboptimal [71,72], and the general consensus for occupational vaccine policy should be considered decisive to promote the safety of HCW and patients [73]. Unfortunately, the policy for HCW appears to be quite different in different European countries **(Table 2)**, as it is mandatory in some region and only recommended or recommended for certain HCW figures in others [74].

Future perspective

Vaccination provides excellent protection against HBV, and the introduction of the recombinant vaccine has allowed its widespread application. A remaining issue is the limited subgroup of the population, the so-called nonresponders. The definition of the Advisory Committee on Immunization Practices for nonresponders is related to 'persons who do not develop protective surface antibodies after completing two full series of the HBV vaccine and for which an acute or chronic HBV infection has been ruled out' [75]. However, recent studies have suggested a way to recognize nonresponders with high precision through the analysis of their antibody levels. In fact, individuals with a titer less than 2 IU/l at the moment of evaluation, independently of the time elapsed since the vaccine, have a higher probability of being nonresponders [24].

Several studies highlight that *HLA* genes and immunoregulatory cytokine gene polymorphisms are involved in nonresponse to recombinant vaccines. These studies will direct as a future goal the engineering of personalized vaccines to overcome the problem of nonresponse.

EXECUTIVE SUMMARY

Hepatitis B prevention

- Nationwide HBV vaccinations have resulted in worldwide reductions of new HBV infections and HBV-related mortality.
- Mandatory vaccination against virus infection covers a wider segment of the population.

Hepatitis B protection

- The two main issues related to HBV vaccination are persistence over time of antibodies and whether the waning or disappearance of antibodies permits a response to viral load.
- A level of antibodies higher than 2 IU/l is predictive of a robust response to a booster dose.
- Nonresponders should be defined after at least two full vaccine series.

Occupational risk

- Healthcare workers have a higher risk of exposure to blood-borne pathogens than the general population.
- Mandatory vaccination should be implemented for healthcare workers.
- Testing for anti-HBs antibodies at the time of recruitment should be routine practice.

The conclusions of the meeting of the Viral Hepatitis Prevention Board held in Barcelona in November 2012 suggest mandatory vaccination of HCW as the only effective means of prevention. The Board suggested that possible future activities should include the following: 'refurbishment of the image of the health profession; resolving the logistical problems of administering vaccine; elaborating policy on managing HVW who have been vaccinated against HBV at birth or in early childhood and who are now starting to work in the health professions; embedding and applying policies on vaccination against vaccine-preventable diseases in all healthcare facilities and training institutions' [76].

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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• **This report is the conclusion of Viral Hepatitis Prevention Board Meeting.**